UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/477989

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/477,989	06/07/95	BAIN	H 61750-147

EXAMINER

18M1/0318

CARELLA BYRNE BAIN GILFILLAN CECCHI
STEWART & OLSTEIN
6 BECKER FARM ROAD
ROSELAND NJ 07068

ART UNIT	PAPER NUMBER
1806	10

DATE MAILED: 03/18/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 11/27/96

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-10 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-10 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. SUBSTITUTE
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 ☑ NOTICE TO COMPLY SEQUENCE
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948 SUBSTITUTE
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The communication filed on 2/28/97 (Paper No. 8) is not fully responsive to the communication mailed 11/2/96 for the reasons(s) set forth on the attached Notice to Comply with the Sequence Rules.

Applicant is required to complete the response in response to this Office Action in the interest of compact prosecution,

2. The drawings submitted with this application were declared informal by the applicant. Accordingly, they have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review.

Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Applicant is reminded of the following if photographs are to be submitted.

Photographs are not acceptable until petition is granted as set forth in 37 CFR 1.84(b). Under 37 CFR 1.84(b), the applicant must file a petition with fee ($130) requesting acceptance of the color and black and white photographs. The petition is decided in the Office of the Group Director.

If color photographs are to be filed, the following is noted. It is anticipated that such a petition will be granted only when the PTO has determined that a color photograph is the only practical medium by which to disclose in a printed utility patent, the subject matter to be patented. The petition must also be accompanied by a proposed amendment to insert the following language as the first paragraph in the portion of the specification containing a Brief Description of the Drawings: The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

3. Content of Specification

(a) Title of the Invention. (See 37 C.F.R. § 1.72(a)). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R. § 1.78 and section 201.11 of the M.P.E.P.

(c) Statement as to rights to inventions made under Federally sponsored research and development (if any): See section 310 of the M.P.E.P.

(d) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of

the claimed invention. This item may also be titled "Technical Field".

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art".

(e) Summary: A brief summary or general statement of the invention as set forth in 37 C.F.R. § 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(f) Brief Description of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R. § 1.74.

(g) Description of the Preferred Embodiment(s): A description of the preferred embodiment(s) of the invention as required in 37 C.F.R. § 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention". Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(h) Claim(s) (See 37 C.F.R. § 1.75): A claim may be typed with the various elements subdivided in paragraph form. There may be plural indentations to further segregate subcombinations or related steps.

(i) Abstract: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less.

There appears to be no Summary of the Invention disclosed in the instant application. Applicant is reminded that no new matter should be added to the specification.

4. The disclosure is objected to because of the following informalities:

Page 23, Example 2 of the specification refers to Appendix 1, however the information indicated in Appendix 1 should be incorporated into body of the specification as a Table or added as a Figure. An Appendix is not proper.

The specification is replete of trademarks. The use of trademarks such as "OKT3", "KETALAR", "PRAZINE", etc. are noted in this application. They should be capitalized and/or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is required to identify the nucleotide and amino acid sequences in the specification with SEQ. ID NOS.

The application is required to be reviewed and all spelling and like errors corrected. Appropriate corrections are required.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The specification is objected to and claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of LO-CD2a is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species LO-CD2a . Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Although applicant has deposited the LO-CD2 antibody or hybridoma (HB 11423) with the ATCC under the Budapest Treaty, there appears no assurances indicated above. Applicant's provision of these assurances would obviate this objection/rejection.

Alternatively, applicant may satisfy the deposit requirement for LO-CD2a if the amino acid sequence of the entire LO-CD2a antibody is disclosed and recited in the claims.

7. Claims 1-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-7 are is indefinite in the recitation of "LO-CD2a" because LO-CD2a refers to a particular antibody produced by the ATCC HB 11423 hybridoma. Applicant should either amend the claim to read "the LO-CD2a antibody produced by the ATCC HB 11423 hybridoma" or recite the appropriate SEQ ID NOS.

B) Claims 1-7 are indefinite in the recitation of "as shown in/of Figure 31/33" because thee are multiple sequences in these figures. In addition, applicant should recite the appropriate SEQ ID NO. for clarity.

C) Claims 8-10 are indefinite in the recitation of "Figure 29" and "Figure 30" because the appropriate SEQ ID NO. directed to the appropriate amino acid sequence would avoid any ambiguity as to which sequence is relied upon.

D) The amendments must be supported by the specification so as not to add any new matter.

8. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

9. Claims 1-8 are rejected under 35 U.S.C. § 103 as being unpatentable over Xia et al. (Rat Hybridomas and Rat Monoclonal Antibodies, 1990; 1449) or Bombil et al. (Cancer Immunol. Immunother., 1995) in view of Queen et al. (U.S. Patent No. 5,530,101. The instant claims are drawn to chimeric and humanized antibodies that bind the LO-CD2 specificity.

Xia et al. provides a number of phenotypic and functional characteristics that are associated with the LO-CD2a specificity (see entire document). Also, Xia et al. distinguishes the LO-CD2a specificity from other CD2-specific antibodies and clearly discloses that this specificity binds a different epitope from other CD2-specific antibodies (for example, see page 320, paragraphs 1-3). It would have been expected at the time the invention was made that different antibodies would recognize the same conformational epitope, which is the LO-CD2 epitope in the instant case. The prior art clearly set forth numerous features that characterize and enable one of skill in the art at the time the invention was made to make an antibody that binds to the same LO-CD2 epitope specificity as claimed.

Similarly, Bombil et al. teaches that LO-CD2-specific antibodies inhibit human inflammatory responses (see entire document).

Queen et al. teaches the art-known procedures at the time the invention was made to produce chimeric antibodies starting from hybridoma and antibody producing cells.

Queen et al. teach that immunoglobulin gene structure and organization were well understood in the art at the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs comprising expression vectors containing DNAs encoding immunoglobulin variable regions. The determination and manipulation of the nucleic acid sequence is an outcome and mechanism of such engineering. Also, it discuss the art-known desirability of

chimeric and humanized antibodies in order to reduce immunogenicity in vivo of therapeutic and diagnostic antibodies in human patients. Queen et al. differs from the claimed invention by not teaching the LO-CD2a specificity per se, the ordinary artisan would have been motivated to apply the teachings of Queen et al. to enable the isolation and construction of chimeric and humanized antibodies that bound the LO-CD2a specificity.

Queen et al. teach that the method of humanizing antibodies in order to reduce immunogenicity while retaining high binding affinity for diagnostic and therapeutic purposes as well as the appropriate vectors, host cells, etc. to accomplish the engineering of chimeric and humanized antibodies (see entire document). The determination and manipulation of the nucleic acid sequence is an outcome and mechanism of such engineering. Although Queen et al. do not teach humanizing the specific antibodies of the instant invention, however, one of ordinary skill in the art at the time the invention was made would have been motivated to do so for any antibody intended for various diagnostic and therapeutic use in humans for the reasons cited above in the previous section. Therefore, from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

It would have prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the LO-CD2a specificity taught by Xia et al. or Bombil et al. in the generally applicable immunoglobulin gene cloning methods taught by primary references in order to obtain DNAs encoding the heavy and light chain variable regions of the LO-CD2a specificity. Having obtained said DNAs it would have been obvious to insert them into suitable expression vectors to express the constructs. One of ordinary skill in the art would have been motivated to do so in view of the above teachings of the advantage of producing chimeric immunoglobulins for in vivo diagnostic and therapeutic regimens in humans to reduce their immunogenicity as well as to produce high level expression of immunoglobulins of interest. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Guckel et al. (J. Exp. Med., 1991; 1449), Bromberg et al. (Transplant., 1991; 1449), Hafler et al. (J. Immunol., 1988; 1449), Chavin et al. (Transplant., 1992; 1449), or Faustman (U.S. Patent No. 5,283,058) in view of Xia et al.(Rat Hybridomas and Rat Monoclonal Antibodies, 1990; 1449) or Bombil et al. (Cancer Immunol. Immunother., 1995) and Queen et al. (U.S. Patent No. 5,530,101). The instant claims are drawn to the inhibition of immune responses such as graft rejection by chimeric or humanized antibodies that bind the LO-CD2 specificity.

Guckel et al., Bromberg et al., Hafler et al., Chavin et al. and Faustman all teach the art-known potent inhibition of immune responses against antigens in vivo by blocking or modulating T cell surface receptors such as CD2 that are important in adhesion receptor-signalling (see entire documents particularly the Introductions and Discussions).

Guckel et al. teach the ability of rat anti-CD2 antibodies to induce T cell unresponsiveness in vivo in mice (see entire document). CD2-specific antibody inhibition of transplants and autoimmunity is taught (page 965, column 2, paragraph 2).

Bromberg et al. teach that anti-CD2 antibodies alter cell-mediated immunity in vivo by altering the array of cell surface receptors and subsequent responses to antigenic challenge (see entire document). Bromberg et al. also teach the potent immunosuppressive properties of anti-CD2 antibodies for murine allografts and xenografts as well as for primate skin and renal allografts (page 224, column 1, paragraph 1).

Hafler et al. teach that anti-CD2 antibodies inhibit T cell responses in human patients with progressive multiple sclerosis (see entire document). Hafler et al. also teach that T cell-specific antibodies have been used successfully as immunosuppressive reagents in transplant rejections and autoimmune diseases (see Introduction).

Chavin et al. teaches the efficacy of treating allografts and xenografts in vivo with CD2-specific antibodies (see entire document, particularly the Introduction and Discussion). Prolonged allograft survival correlated with suppression of both CTL and NK activity (page 290, column 1, paragraph 3 and Table 2). Here, Chavin et al. concludes by stating that the ability of anti-CD2 antibodies to suppress lymphocyte precursors and T and non-T cell responses supports its use for induction therapy in transplantation.

Faustman teaches methods of inhibiting the rejection of allografts and xenografts with T cell-specific antibodies and antibody fragments including the CD2-specificity (see entire document, including column 5, paragraph 1). Such methods of inhibiting rejection include modifying, eliminating and masking an antigen on the surface of a cell (see entire document, including Abstract).

Therefore, it was known at the time the invention was made that the CD2-expressing T cells and NK cells were involved in a number of immunoregulated diseases and that CD2-specific antibodies could immunosuppress such effects in vivo in various systems. These references all teach the role of inhibiting immune responses associated with the claimed limitations of T cells, NK cells, autoimmunity, GVHD, allografts and xenografts through CD2-specific antibodies. Administering the antibody intravenously as a pharmaceutical agent was well known to the ordinary artisan at the time the invention was made. Similarly, treating grafts including organs prior to transplantation to rid such tissues of passenger leukocytes was well known to the ordinary artisan at the time the invention was made.

These references differ from the instant invention by not teaching the particular LO-CD2 or LO-CD2a specificity per se.

As indicated above in section 9, the combined teachings of Xia et al. or Bombil et al. and Queen et al. teach chimeric and humanized antibodies that bind the LO-CD2a specificity of the instant invention and its ability to inhibit lymphocyte function. Xia et al. does teach the benefits of producing rat anti-human monoclonal antibodies for clinical therapeutic use (see page 310, paragraph 1).

One of ordinary skill in the art at the time the invention was made would have been motivated to select the efficacy of the LO-CD2 specificity as diagnostic and therapeutic regimens to inhibit T cell adhesion activation and function in various human diseases including autoimmunity and transplantation. It would have been obvious at the time the invention was made to generate chimeric and humanized antibodies From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

32. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (30-63) and (30-63) of copending application Serial Nos. 08/472,281 and 08/477,877, respectively. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to same or similar chimeric and humanized LO-CD2-specific antibodies.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-10 are directed to an invention not patentably distinct from claims (30-63) and (30-63) of copending application Serial Nos. 08/472,281 and 08/477,877, respectively. Specifically, the conflicting claims are patentably distinct from each other because both applications are drawn to same or similar chimeric and humanized LO-CD2-specific antibodies.

Commonly assigned 08/472,281 and 08/477,877, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 17, 1997